John D. Boice, Jr.
Peter D. Inskip

C H A P T E R

11

Radiation-Induced Leukemia

HISTORICAL BACKGROUND

A new era began in 1895 when Roentgen discovered "a new kind of ray" that could penetrate the human body and reveal broken bones. The first x-ray film was taken in 1896, the same year that uranium was found by Becquerel to be naturally radioactive. The first radiation-induced skin cancer was reported in 1902 and appeared on the hand of a roentgenologist. Reports of excess leukemia among radiologists appeared in the 1940s, and radiation-induced leukemia is believed to have caused the death of Madame Curie and her daughter Irene. Patients treated with radiation for benign diseases in the 1930s to the 1950s were subsequently found to be at high risk for leukemia. The studies of Japanese atomic bomb survivors began in 1950 and have provided substantial knowledge on radiation effects. Radiation is perceived by the public as a major carcinogen despite convincing evidence that it contributes only a small amount to the overall cancer burden. This perception likely comes from images of wartime uses of nuclear weapons and, more recently, reactor accidents such as Chernobyl. Although radiation is a near-universal carcinogen, it is a weak one, in part because it is an especially good killer of cells. We live in a sea of low-level natural radiation from terrestrial and cosmic sources, and our bodies have developed repair mechanisms to correct damage following such exposures. Leukemia, although a rare disease, is the most frequently reported malignancy following radiation exposures.[96,138]

BASIC CONCEPTS

Energy emitted from a source is generally referred to as radiation. Examples include heat or light from the sun, radio signals from a transmitting antenna, microwaves from an oven, x-rays from an x-ray tube, or gamma rays from radioactive elements. Radiation of sufficient energy to remove electrons from atoms is called *ionizing* radiation and includes electromagnetic rays such as x-rays and gamma rays and energetic particles such as protons, fission nuclei, and α– and β– particles. Neutrons, unlike these other particles, have no charge and cannot ionize directly. Instead they impart energy to protons through elastic collisions,

and the protons then cause subsequent ionizations. Another way in which energy can be released in tissue is by *excitation,* whereby electrons are merely raised to a higher energy level within an atom but are not removed. The total amount of energy absorbed in matter as a result of radiation interactions is called the dose, which is measured in gray (Gy): 1 Gy = 1 Joule per kilogram. Until recently, the standard unit for dose was the rad (1 rad = 100 ergs per gram), but the conversion is simple: 1 Gy = 100 rad = 100 cGy. An acute whole-body dose of about 5 Gy (500 rad) is lethal about half of the time in humans; yet, this dose ionizes only about 1 of every 40 million molecules. Thus, permanent damage can be produced after a relatively small amount of energy is absorbed.

Radiation is absorbed randomly by atoms and molecules in cells and can alter molecular structure. These alterations can be amplified by biologic processes to result in observable effects. The biologic effects, however, depend not only on the total absorbed dose but also on the linear energy transfer (LET), or ionization density, of the type of radiation. LET is a measure of the energy loss per unit distance traveled and depends on the velocity, charge, and mass of a particle or on x-ray or gamma-ray energy. High-LET radiations such as α– particles (helium nuclei) release energy in short tracks of dense ionizations. Low-LET, or sparsely-ionizing, radiations such as x-rays or gamma rays produce ionization events that are not close together. Depending on the biologic endpoint, the effect per Gy may differ widely as a function of LET but is usually lower for low-LET radiation.

In experimental studies, the induction of many cancers following low-LET radiation appears to follow a nonlinear relationship with dose, with risk per unit dose being lower at low doses than at high doses.[98] Chronic exposures also result in fewer leukemias than brief exposures of the same total dose.[141] The induction of cancer by exposure to high-LET radiation has generally appeared to follow a linear dose response. Moreover, protraction and fractionation of dose from high-LET radiation tend not to decrease cancer risk but rather to increase it somewhat, especially at higher dose levels, because of a reduction in the competing effect of cell killing.[138a] Recent studies suggest that this enhancement of risk at lower dose rates may also occur at levels at which cellular killing is minimal.

The relative biologic effectiveness (RBE) of radiation characterizes its ability to produce a specific disorder (e.g.,

chromosome aberration, cell death, or cancer) compared with a standard, usually x-rays or gamma rays. An RBE of 20 for α– particles at 10 cGy, for example, would imply that the biologic effect from 10 cGy of α– particles is the same as that from 200 cGy of gamma rays. The unit of biologic dose equivalence used in radiologic protection is the sievert (Sv), which has replaced the rem (1 Sv = 100 rem). The sievert represents the absorbed dose in Gy, multiplied by a quality factor (specific to the type of radiation) and other possible modifying factors. The sievert also has been applied to assess the effects of exposures to more than one type of radiation. For example, the dose equivalence of an exposure to 10 cGy of gamma rays plus 10 cGy of α– particles, with gamma rays as the standard and an RBE of 20 for α– particles, would be 2.1 Sv (210 rem).

SOURCES OF EXPOSURE

Background radiation from natural sources contributes the most to population exposure, about 2.9 mSv per year (0.29 rem) (Table 1l–1).[96, 138] These sources include cosmic rays (0.27 mSv/year), which vary by altitude; terrestrial radiations (0.28 mSv/year), which vary according to the distribution in soil and bedrock of radioactive elements such as uranium; internally deposited radionuclides such as ^{40}K (0.39 mSv/year); and radon (2.0 mSv/year and confined mainly to lung). The greatest artificial source of radiation is medical procedures (0.53 mSv/year), with exposures increasing directly with patient age. Nuclear medicine procedures are estimated to contribute 0.14 mSv/year average effective dose to the population. Occupation, nuclear power, fallout from testing nuclear weapons, and consumer products make only a minor contribution (0.11 mSv/year). The average per capita dose from all sources of radiation, excluding radon, is thus about 1.6 mSv (0.160 rem) per year. Some individuals in the population, however, can experience much higher exposures, such as cancer patients treated with radiation.

On the basis of studies of Japanese atomic bomb survi-

Table 11–1
ANNUAL POPULATION EXPOSURES TO IONIZING RADIATION

Source	Annual Dose (mSv)*
Natural sources	
Cosmic, terrestrial, internal	0.94
Radon	2.00 (mainly to lung)
Medical	
X-ray diagnosis	0.39
Nuclear medicine	0.14
Consumer products	0.10
Other	
Occupational	<0.01
Nuclear fuel cycle	<0.01
Fallout	<0.01
Miscellaneous environmental sources	<0.01
Total (excluding radon)	1.6

*1 mSv = 0.1 rem, annual effective dose equivalent

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vors, the lifetime risk for developing leukemia after acute whole-body exposures of 1 Gy is estimated to be 85 per 10,000 persons (or 0.85 percent). Continuous lifetime exposure of 100,000 persons to 1 mSv/yr has been estimated to induce about 65 leukemias.[96] If true, then 3 to 5 percent of all leukemias might be attributable to all sources of radiation exposure (1.6 mSv/yr). Although radiation has clearly been found to cause leukemia in humans, there remain substantial uncertainties as to the level of risk from low doses delivered at low dose rates. At doses under approximately 0.1 Gy, the risks appear too low to be detected, and extrapolations from high-dose studies are performed to estimate possible risks.

MECHANISMS

Ionizing radiation is relatively ineffective at inducing point mutations in DNA but is effective at inducing DNA strand breaks.[97] Most single-strand breaks are rapidly repaired, but double-strand breaks can result in chromosomal rearrangements, including translocations, inversions, additions, and deletions. Such aberrations, if not lethal, can lead to cancer through changes in expression of normal genes; the formation of new, chimeric genes; and the loss or inactivation of genes inhibitory of tumorigenesis.[123]

Cytogenetic and molecular studies have clearly demonstrated that many forms of leukemia and lymphoma are associated with specific chromosomal rearrangements, at least some of which appear to result in the activation of proto-oncogenes and are believed to be central to the pathogenesis of these diseases[25, 112, 116 123] (see Chapters 3 and 7 for details). This is in contrast to most epithelial cancers, for which the loss or inactivation of so-called tumor suppressor genes appear to be more generally important.[88] For leukemia, the paradigmatic case is the Philadelphia (Ph) chromosome, which is seen in leukemic cells of more than 90 percent of persons with chronic myelogenous leukemia (CML).[113] It results from a reciprocal translocation involving chromosomes 9 and 22.[101, 113] Part of the Abelson proto-oncogene, ABL, on chromosome 9 is cleaved and then fused with the *BCR* gene on the long arm of chromosome 22, resulting in the chimeric gene, *BCR-ABL*. The protein product of the fused gene is a tyrosine kinase.[65] Molecular evidence of chimeric *BCR-ABL* genes also was seen in cytogenetically normal (Ph chromosome–negative) CML patients,[143] which lends credence to the view that this genetic change is causally involved in the pathogenesis of the disease rather than incidental to it. The Ph chromosome also is the most common cytogenetic abnormality seen in adults with acute lymphoblastic leukemia (ALL), although a variety of other rearrangements, including t(8;14) and t(4;11), have been noted in a high percentage of cases of ALL.[15] Different translocations have been associated with other forms of leukemia, including t(8;21) in acute myeloblastic leukemia, t(15;17) in acute promyelocytic leukemia, and t(10;11) and t(9;11) in acute monoblastic leukemia.[116]

The spectrum of chromosomal abnormalities observed in leukemias arising following cytotoxic therapy is reported to differ from those arising de novo, that is, among persons lacking known exposure to a strong mutagenic agent. Par-

tial or total losses of chromosomes 5 and 7 were seen in myeloid cells from a high percentage of persons who developed acute nonlymphocytic leukemia or myelodysplastic syndrome following combined radiotherapy and chemotherapy for a primary malignancy.[115] Growth factor and growth factor receptor genes are located on chromosome 5, but it is not known whether they play an etiologic role in leukemogenesis.[114] Moloney[93] reported that the mix of acute leukemia subtypes seen among irradiated cervical cancer patients and atomic bomb survivors was similar to the mix seen among patients with de novo disease; however, a different array of leukemic cell types was noted among persons previously irradiated for ankylosing spondylitis.

Whether the nonrandom chromosomal translocations, deletions, and other rearrangements seen for the different types of leukemia reflect the existence of fragile sites within the chromosomes[153] or selective clonal growth following randomly distributed damage is uncertain. Silver and Cox (1993) reported evidence of a genetically determined predisposition to radiation-induced acute myelocytic leukemia (AML) in a particular strain of mice.[119a] Susceptibility to AML appeared to be related to a polymorphism invoking DNA sequences on chromosome 2 that are prone to breakage by ionizing radiation. Breckon and colleagues[16, 17] conjectured that fragile sites on the long arm of chromosome 5 might play a role in human radiation leukemogenesis analogous to the radiation sensitive sites on the murine chromosome 2.

Lymphoid malignancies show their own characteristic set of rearrangements.[25, 119, 116] B-cell and T-cell tumors often exhibit translocations that place cellular oncogenes in the vicinity of immunoglobulin (IG) or T-cell receptor genes, resulting in proto-oncogene activation through transcriptional deregulation.[119] The best-known example is the t(8;14) translocation seen in Burkitt's lymphoma, which results in the juxtaposition of the *MYC* proto-oncogene with IG genes and consequent aberrant expression of *MYC*.[75] A high percentage of non-Burkitt's B-cell tumors, including CLL, diffuse lymphomas, and multiple myeloma also show translocations involving the 14q band containing the locus for IG heavy chains.[25] Interestingly, however, with the exception of ALL, cancers of lymphoid cells have not been convincingly linked to radiation exposure. In particular, chronic lymphocytic leukemia (CLL) has not been found to be associated with irradiation in any major epidemiologic study.[9, 26, 28, 60, 106] Studies of the atomic bomb survivors also failed to detect an association between radiation dose and incidence of adult T-cell leukemia, a disease in which the HTLV-1 virus is thought to play a causal role (see Chapters 9 and 26).[106] Whether or not radiation causes lymphoma and myeloma remains an unresolved question.[8]

In summary, ionizing radiation is a clastogen that deposits energy at random in tissues, and chromosomal rearrangements appear to be causally involved in the pathogenesis of cancers of myeloid and lymphoid cells. Yet, susceptibility to radiation-induced cancer appears to vary widely among different subsets of marrow-derived cells. This underscores the importance of lineage-specific developmental processes and, perhaps, the heterogeneity of progenitor cell populations for blood cell malignancies (see Chapter 3).[48] Those cancers most closely associated with exposure to ionizing radiation, namely CML, AML, and,

perhaps, some types of ALL, as well as several preleukemic syndromes, apparently originate in primitive multipotential stem cells.[48] CLL, lymphoma, and multiple myeloma, on the other hand, are thought to arise from mature, differentiated lymphoid cells.[48] One would nonetheless expect radiation-induced genetic damage in a pluripotent stem cell to be propagated to descendants that differentiate along the lymphoid line. Why this would not be related to increased cancer risk is unclear. Perhaps the balance between cellular transformation and inactivation as a function of radiation dose differs between lymphoid cells and those of other lineages. Alternatively, other genetic changes or developmental events, possibly immunologic in nature, might be rate-limiting to cancer development in cells committed to this lineage.

In light of recent public concern over the possibility that *nonionizing* electromagnetic fields might also cause leukemia and other types of cancer, it should be noted that no evidence of chromosomal breakage or other mutations has been found in experimental studies involving low-frequency electromagnetic fields.[102] If nonionizing radiation does indeed cause leukemia, and the evidence for this is far from persuasive, it seemingly must do so through a fundamentally different mechanism than ionizing radiations.

HUMAN STUDIES OF RADIOGENIC LEUKEMIA

Leukemia is the most commonly identified cancer following irradiation, probably because of its short minimum appearance time, its relatively low natural incidence, and the high radiation sensitivity of active marrow. Radiogenic leukemia has an early onset, with the minimal latency being about two years. The subsequent pattern of excess risk over time is wavelike. Excess leukemias have occurred among populations exposed as a result of military circumstances, occupational endeavors, medical care, and environmental situations (Table 11–2).[138]

Nuclear Weapons Use and Testing

Japanese Atomic Bomb Survivors

For over 40 years, The Radiation Effects Research Foundation in Japan has studied the survivors of the atomic bomb detonation that occurred during World War II.[103] This single study has provided more information on radiation risks than any other. The Leukemia Registry was established in 1948, and the first report of radiogenic leukemias appeared in 1952.[41] The most recent analyses in the Life Span Study sample include 253 cases of leukemia.[106] Compared with other tumors, leukemia has one of the highest relative risk (RR) coefficients. At 1 Gy (100 rad) whole-body exposure, a six-fold risk is estimated, whereas it is 1.29 for all other cancers combined. Over half of leukemias occurring among the atomic bomb survivors are attributed to radiation.[118] It has been suggested that the temporal pattern of risk varies with age at exposure, with those exposed at younger ages having a higher peak and a

Table 11–2

EPIDEMIOLOGIC STUDIES OF POPULATIONS EXPOSED TO IONIZING RADIATION AND SUBSEQUENT RISK OF LEUKEMIA BY TYPE OF EXPOSURE AND STRENGTH OF ASSOCIATION

Type of Exposure	Study	Strength of Association*
Atom bomb	Japanese survivors[106]	+ + +
Radiotherapy		
Malignant disease	Cervical cancer[9]	+ +
	Endometrial cancer[26]	+ +
	Breast cancer[27]	+ +
	Hodgkin's disease[136]	+
	Non-Hodgkin's lymphoma[135]	+
	Childhood cancer[137]	—
Benign disease	Ankylosing spondylitis[31]	+ + +
	Menstrual disorders[60]	+ + +
	Scalp ringworm[111]	+
	Peptic ulcer[50]	+
Diagnostic x-ray studies	Tuberculosis fluoroscopy[33]	—
	General radiography[12]	±
	Prenatal x-ray[134]	±
Radionuclides	I-131[38, 51]	±
	Thorotrast[2]	+ +
	Radium[126]	—
	P-32[3]	+
Occupation	Radiologists[148]	+ +
	Nuclear energy workers[47, 86]	±
	Radon-exposed miners[133]	—

  * + + + = highly significant finding; + + = meaningful association; + = suggested but unconfirmed; ± = equivocal; — = no evidence for an increased risk.

Figure 11–1

Schematic diagram of the temporal pattern of leukemia risk among atom bomb survivors according to age at exposure and cell type. (From Okada S, Hamilton HB, Egami N, et al (eds): A review of thirty years of Hiroshima and Nagasaki atomic bomb survivors. J Radiat Res Tokyo, 1975, 16 (Suppl), 1–164.)

more rapid decline than those exposed in later life (Fig. 11–1).

Over 60 percent of the leukemia cases have been reclassified using the French-American-British nomenclature, and radiation risk is seen to vary by cell type. Few diagnoses of CLL have been made, and there is no evidence in this or any other study that radiation causes CLL. The risk of CML was high, and a wavelike time response evident, especially in Hiroshima. CML has been thought to be the most characteristic leukemia of the atomic bomb survivors. The high risk in Hiroshima was once attributed to neutrons but is now thought to be related more to the higher naturally occurring rate in Hiroshima than in Nagasaki. AML, with over 100 cases, is the most common leukemia, with excesses occurring at all ages. The radiation risk for ALL was somewhat higher than that for AML and decreased more rapidly; the excess of ALL also occurred predominantly among younger survivors. No association with radiation was found for the 30 cases of adult T-cell leukemia (ATL).

The risk of leukemia among atomic bomb survivors also was seen to increase with radiation dose (Fig. 11–2). A suggested downturn after 4 Gy may be due to cell killing of stem cells. The best-fitting dose-response model is linear-quadratic, which implies that risk per unit exposure at low dose is less than that at higher doses. However, dose response and risk estimates varied by subtype, age, time, and sex (Table 11–3), so that comparisons with other studies or generalizations to other populations must be done cautiously. Characterizing any single study population in terms of summary relative or absolute risk coefficients tends to obscure these important differences.
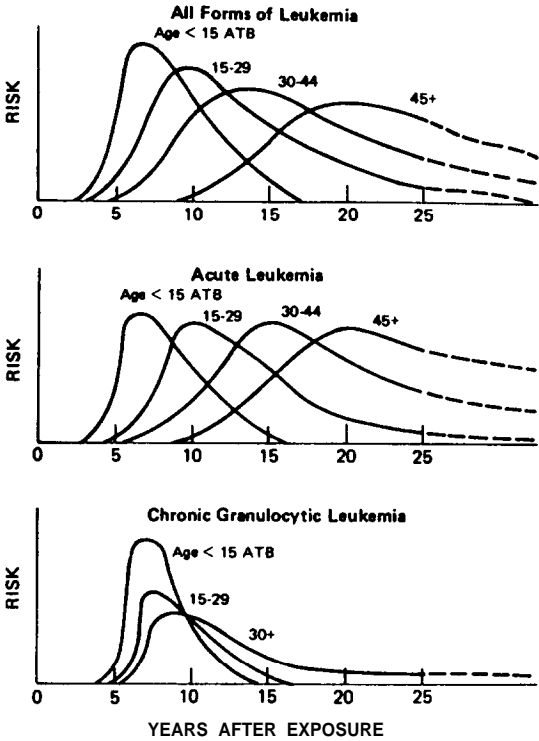
Leukemia has not been linked to in utero or preconception exposure in the atomic bomb study.[61, 100] Among the 1630 individuals exposed in utero, no childhood leukemias occurred; two cases of adult leukemia were diagnosed in individuals aged 18 and 29. Both patients received less than 0.05 Gy (5 rad), and there was no evidence of a dose-response relationship.[152]

With regard to possible germline effects, 44 cases of leukemia have been diagnosed among 76,000 offspring of the atomic bomb survivors (F_1 cohort) as of 1985.[100] Only three cases of leukemia occurred among children born in
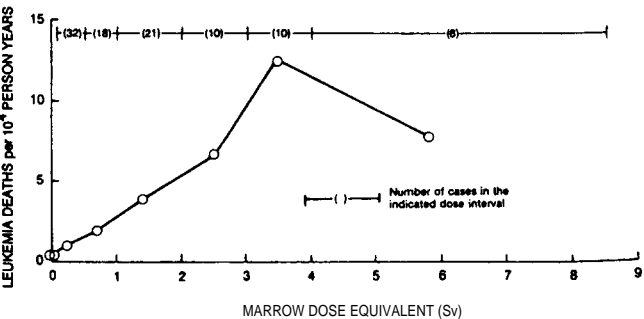

Figure 11–2

Leukemia dose-response relationship seen among Japanese atom bomb survivors, (From NAS [National Academy of Science]: Health Effects of Exposure to Low Levels of Ionizing Radiation [BEIR V]. Washington, D.C., National Academy Press, 1990. Reprinted with permission from Health Effects of Exposure to Low Levels of Ionizing Radiation. Copyright 1990 by the National Academy of Sciences. Courtesy of the National Academy Press, Washington, D.C.)

Table 11–3

RELATIVE RISK ESTIMATES FOR RADIATION-INDUCED LEUKEMIA AMONG ATOMIC BOMB SURVIVORS BY SEX, AGE AT EXPOSURE, AND TIME SINCE EXPOSURE

Characteristic	Exposed Cases		Mean Dose (Gy)	Relative Risk at 1 Gy	Excess Absolute Risk*
	Observed	*Expected*			
Sex					
Male	71	35.3	0.26	4.91	3.35
Female	70	32.1	0.25	5.75	2.29
Age at exposure (yr)					
<20	46	17.9	0.26	7.11	2.28
≥20	95	49.5	0.25	4.70	3.06
Time since exposure (yr)					
5–10	29	5.1	0.25	19.7	5.87
11–20	45	40.3	0.25	1.46	0.50
21–30	34	18.5	0.25	4.32	2.21
31–42	33	28.1	0.25	1.70	0.75
All	141	67.4	0.25	5.37	2.73

*Excess leukemia cases per 10,000 persons per year per gray (10^4PY-Gy).

From Preston D, Kusumi S, Tomonaga M, et al: The incidence of leukemia, lymphoma, and myeloma among A-bomb survivors, 1950–87. Radiat Res, 1994, 137(Suppl), S68–s97.

1946. These numbers were not in excess of expectation, and there was no evidence of a radiation effect in any of these groups. Thus, there was little evidence that parental exposure to radiation causes an increased susceptibility to leukemia in offspring among atomic bomb survivors. This is in contrast to a study in the United Kingdom, which reported an association of childhood leukemia with paternal exposure prior to conception at a nuclear-fuel reprocessing plant in Sellafield, England. Subsequent studies around Scottish and Canadian nuclear plants, however, have failed to provide corroborative evidence of a preconception effect.[76, 86]

Despite the singular importance of the Japanese atomic bomb survivor studies with respect to our understanding of radiation leukemogenesis and for radiation risk estimation, it provides no information on the effects of fractionated or low-dose–rate exposures such as experienced in occupational or medical settings, or about the effects of high-dose partial-body exposures such as experienced in radiotherapy.

Fallout in Utah from Weapons Tests

Aboveground nuclear weapons testing in the 1950s and 1960s resulted in radioactive fallout exposures to populated areas in the United States. A recent case-control study of over 1000 individuals who died of leukemia in southwestern Utah, near the Nevada test site, identified a weak positive association between estimated bone marrow dose and total leukemia, although the trend was not significant.[128] Significant risks, however, were observed for acute leukemia among those under age 20 when exposed to fallout, similar to estimates obtained from other studies of exposed populations. The increasing trends seen for CLL, a tumor not known to be elevated after irradiation, and the difficulty in estimating doses retrospectively are reasons for caution in interpretation.

Fallout in Nordic Countries

Secular trends in childhood leukemia within Nordic countries were evaluated for possible changes that might be related to fallout from atmospheric nuclear weapons testing in the 1950s and 1960s.[31] Estimates of fetal bone marrow exposure, primarily from cesium 137 (^{137}Cs), were about 0.14 mSv, and no increase in leukemia incidence could be tied to such levels. A seven-year cumulative exposure was estimated to be 1.5 mSv. There was no evidence for a preconception effect based on estimated paternal testicular dose. These data suffer from the same uncertainties as all ecologic surveys, in that doses to individuals are unknown. Further, there have been a great many other environmental and social changes since World War II other than low-level radioactive fallout that might influence the incidence, diagnosis, and reporting of leukemia over time.

Fallout in Marshall Islands

Residents of four atolls east of Bikini Island were exposed to nuclear fallout from a United States weapons test in 1954. Significant excesses of thyroid neoplasia have occurred. One case of AML was diagnosed in a 19-year old man who was one year of age when exposed.[22]

Participants at Nuclear Weapons Tests in Nevada

No excess in total cancer mortality (112 versus 117.5) was found among 3017 of 3217 participants in military maneuvers during the 1957 nuclear test called SMOKY.[18] Leukemia, however, was significantly elevated; 10 cases were observed, including the index case that prompted the investigation and one case that developed after radiation therapy for lymphoma, versus 4.0 expected based on rates from the general population. Lower cancer frequencies were generally noted among the military units with the

highest exposures based on film badge doses (mean, 0.46 cGy). A survey of 46,186 military participants in two weapons test series conducted at the Nevada Test Site and three in the Pacific Ocean also found no excess of nonleukemia deaths (990 versus 1187).[108] Excluding SMOKY, 46 leukemia deaths occurred versus 52.4 expected, suggesting that the leukemia excess among SMOKY participants was either due to chance or to circumstances peculiar to that shot (or its participants).

Participants at Nuclear Weapons Tests from the United Kingdom

Cancer mortality and incidence among 21,358 participants in the United Kingdom's atmospheric nuclear weapons tests in Australia and the Pacific Ocean between 1952 and 1967 and in 22,333 matched controls were recently evaluated.[30] Mortality from all causes and from all cancers were similar between the two study groups. Death due to leukemia occurred significantly more often among participants than among controls. Mortality from leukemia among participants, however, was equal to that predicted from national rates (RR = 1.0 based on 29 deaths) but was extremely low among controls (RR = 0.56 based on 17 deaths). Thus, the increased risk of leukemia was related more to a significant deficit among the controls than to an excess among the exposed.

Medical Irradiation

Studies of patient populations irradiated for malignant[14] and benign diseases have provided valuable information on the influence of dose rate and partial-body exposure on leukemia risk. Scatter radiation to organs outside the treatment fields permits the evaluation of relatively low-dose effects. Dosimetric and analytic methods have been developed to evaluate the complex nature of high-dose, nonuniform irradiation of bone marrow in a way that accounts for this heterogeneity.

Malignant Disease

CERVICAL CANCER

To learn about the effects of high-dose radiation delivered to small volumes of tissue and low-dose scatter radiation received by other parts of the body, an international study was conducted of over 100,000 women with cervical cancer who were treated in any of 15 countries. For the first time, a small but significant excess of leukemia was found following radiation treatment for cervical cancer. The wavelike pattern of risk over time was consistent with the study of atomic bomb survivors (Fig. 11–3), but the crude estimate of radiation risk was an order of magnitude lower.[10]

In a subsequent case-control study, CLL was not linked to radiation; but a two-fold risk was seen for acute and chronic myelogenous leukemias.[9] Again, a RR of about 30 would have been predicted based on the average dose received and risk estimates derived from the atomic bomb
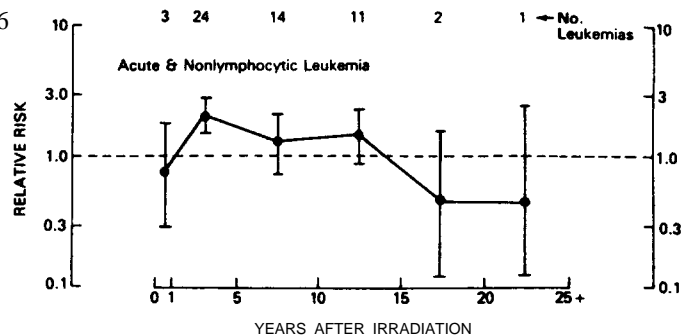

Figure 11–3

Characteristic wavelike pattern of leukemia risk over time since exposure seen among women treated with radiation for cervical cancer. (From Boice JD Jr, Day NE, Andersen A, et al: Second cancers following radiation treatment for cervical cancer. An international collaboration among cancer registries. J Natl Cancer Inst, 1985, 74; 955–975.)

study. Based on actual radiotherapy records and simulated treatments involving measurements in anthropomorphic phantoms, estimates of dose to active bone marrow were made. Doses to 14 different bone marrow compartments were estimated, and the risk of leukemia was modeled taking into account the nonuniform dose distribution from this partial-body exposure. The leukemia risk increased up to doses of approximately 4 Gy (400 rad), and then decreased at higher levels, suggesting that cell-killing might predominate over transformation at very high doses (Fig. 11–4). A similar dose response was observed for radiation-induced chromosomal aberrations in circulating lymphocytes among irradiated cervical cancer patients.[71] High-dose cell killing seems a likely explanation as to why radiotherapy to treat cancer is so infrequently linked to secondary leukemia, and when it is, it is usually at a very low level. In the most heavily irradiated marrow, potentially leukemic cells are inactivated or killed, and in marrow remote from the direct radiation field, relatively few cells are transformed.[58]

ENDOMETRIAL CANCER

In an attempt to replicate the cervical cancer study, over 200 cases of leukemia occurring in a study population of
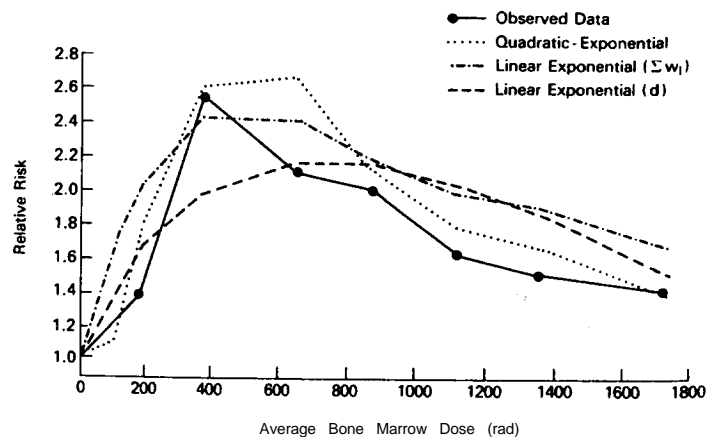

Figure 11–4

Leukemia dose-response relationship seen among women treated with radiation for cervical cancer. (From Boice JD Jr, Blettner M, Kleinerman RA, et al: Radiation dose and leukemia risk in patients treated for cancer of the cervix. J Natl Cancer Inst, 1987, 79; 1295–1311.)

110,000 women with endometrial cancer were evaluated with similar methods.[26] Results were remarkably consistent with the cervical cancer findings. There was a nearly two-fold risk observed for the acute and myelogenous leukemias, and no risk for CLL. Increased risks of leukemia were found among the elderly exposed after the age of 65 years. Overall, however, the pattern of risk by dose was erratic and consistent with a flat dose-response relationship. Interestingly, the risk following continuous exposures from brachytherapy at comparatively low doses and low dose rates (RR = 1.8; mean dose, 1.7 Gy) was similar to that after fractionated exposures at much higher doses and higher dose rates from external beam treatments (RR = 2.3; mean dose, 9.9 Gy). Again, the relationship of leukemia risk to radiation dose was complex and likely due to the competing processes of cellular killing, transformation, and repair. At very high doses given at high dose rates, destruction of cells likely dominates and the risk per unit dose is low. In the low-dose range, at which dose was protracted and given at relatively low-dose rates, the leukemia risk appears to be somewhat lower than that projected based on the instantaneous whole-body exposures received by the atomic bomb survivors (Fig. 11–5).

BREAST CANCER

In a study of nearly 80,000 women with breast cancer, a two-fold risk of leukemia was linked to adjuvant radiotherapy, which included substantial exposure to the chest wall, and there was evidence of a radiation dose response.[27] Chemotherapy was associated with a 10-fold risk, which supports the notion that alkylating agents are much more potent leukemogens than radiation. It appeared that the two treatment modalities interacted with each other in a more than additive manner, and the data were consistent with a multiplication of risks, that is, RR = 17 if both radiotherapy and systemic chemotherapy were given.

LYMPHOMAS

The most serious consequence of curative therapies for lymphoma is the heightened risk of developing a new cancer.[7] However, only small increases in leukemia risk have been reported after radiotherapy alone for Hodgkin's disease.[64, 132, 136, 145] Radiotherapy for non-Hodgkin's lymphoma (NHL), however, has been correlated with excess leukemia.[134, 135] Total or hemibody irradiation for NHL, a unique treatment that exposes large volumes of bone marrow to relatively low therapeutic doses, also was seen to heighten the subsequent risk of leukemia.[49]

CHILDHOOD CANCER

Radiotherapy was not found to increase the risk of leukemia in one study of children treated for cancer,[137] possibly because of the predominance of cell killing over oncogenic transformation at such high levels. A more recent study reported a leukemia risk following radiotherapy,[54] possibly due to associated or interactive effects with chemotherapeutic agents. Children treated for retinoblastoma are at high risk of radiogenic bone cancer due to an underlying genetic susceptibility, but no excess leukemia has been reported.[35, 39]

Benign Disease

BENIGN GYNECOLOGIC DISORDERS

In a recent cohort study of 12,955 women treated for benign gynecologic disease, a significant excess of leukemia death was observed following pelvic radiotherapy administered to stop uterine bleeding.[60] Such treatment was fairly common during the 1930s and 1940s. Most women were in their mid to late 40s at the time of treatment. Interestingly, the average bone marrow dose was a factor of 10 lower than that for uterine cancer treatment (about 0.7 Gy versus 7 Gy), but the RRs were about the same, two-fold. Again, this suggests the importance of cellular killing or inactivation in defining dose-response relationships. Time-response patterns differed for CML and acute leukemia. Similar to the study of atomic bomb survivors (see Fig. 11–1), the excess mortality rate due to CML was concentrated within the first 15 years following irradiation, whereas the relative excess of acute leukemia was more evenly distributed over time. Another recent mortality study of 2067 women irradiated for menstrual conditions in Scotland also revealed a two-fold risk of leukemia (n = 12) associated primarily with external beam therapy (mean dose 1.3 Gy).[32] Risk remained elevated after 30 years of follow-up in both studies.

ANKYLOSING SPONDYLITIS

The mortality experience of 14,558 persons treated between 1935 and 1954 in 87 British radiotherapy clinics for
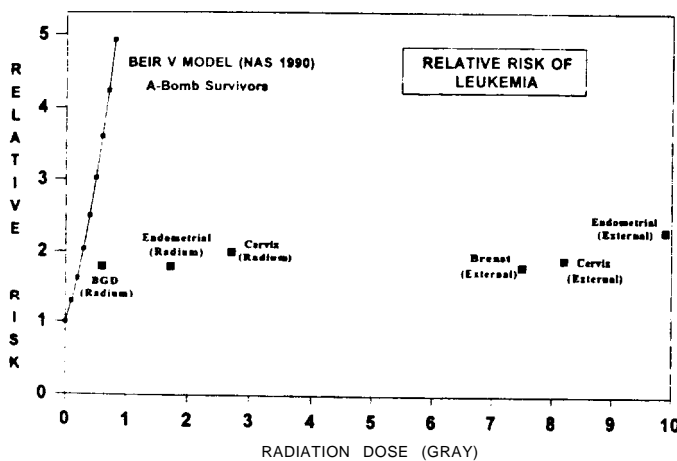

Figure 11–5

Risk of leukemia for several studies of medically irradiated populations compared with Japanese atom bomb survivors according to average dose to bone marrow. (Data from NAS [National Academy of Science]: Health Effects of Exposure to low Levels of Ionizing Radiation [BEIR V]. Washington, D.C., National Academy Press, 1990; Boice JD Jr, Blettner M, Kleinerman RA, et al: Radiation dose and leukemia risk in patients treated for cancer of the cervix. J Natl Cancer Inst, 1987, 79; 1295–1311; Inskip, PD, Kleinerman RA, Stovall M, et al: Leukemia, lymphoma and multiple myeloma after pelvic radiotherapy for benign disease. Radiat Res, 1993, 135, 108–124; Curtis RE, Boice JD Jr, Stovall M, et al: Risk of leukemia after chemotherapy and radiation treatment for breast cancer. N Engl J Med, 1992, 326; 1745–1751; and Curtis RE, Boice JD Jr, Stovall M, et al: Relation of leukemia risk to radiation dose after cancer of the uterine corpus. Natl Cancer Inst, 1994, 86, 1315–1324.)

ankylosing spondylitis, a rheumatoid condition of the spine, has been carefully evaluated.[29] Radiation doses were estimated for each leukemia fatality and for a 7-percent sample of the population and averaged about 3.8 Gy for the active bone marrow. Leukemia risk (47 observed versus 36.1 expected) peaked 3 to 5 years after radiotherapy and gradually declined but not to baseline levels; CLL was not increased (2 observed versus 2.4 expected). The dose response for leukemia was irregular and essentially flat, possibly reflecting reduced leukemogenesis in the most heavily irradiated portions of the marrow due to cell killing or to the fractionated nature of the exposures.[92, 120] Compared with general population rates, the RR of leukemia can be estimated as 1.53 at 1 Gy and the absolute excess risk as $0.38/10^4$ Person-Years (PY)-Gy.

TINEA CAPITIS

In the 1940s and 1950s, radiation was often used to treat nonmalignant conditions, such as ringworm of the scalp. In this circumstance, estimated doses from ringworm treatments were on the order of 1 to 2 Gy to the cranium, and 0.3 Gy averaged over marrow in the entire body. A small excess of leukemia mortality was found among 10,000 children exposed in Israel, indicating that partial-body, relatively low-dose radiotherapy to the head can increase leukemia risk, at least following childhood exposures.[111]

PEPTIC ULCER

In a survey of 1831 patients with peptic ulcer treated with radiation (stomach dose, 16 Gy) and 1778 nonexposed ulcer patients, a small but significant increase in leukemia was observed on 11 cases.[50]

Diagnostic Radiology

Studies of diagnostic radiology and leukemia risk include tuberculosis patients receiving repeated chest fluoroscopies, patients receiving x-ray studies for diagnostic purposes, and children born after being exposed to prenatal x-ray studies. The doses associated with diagnostic procedures are generally small, and the possible risk is accordingly low and difficult to detect. It is estimated that only a small percentage of leukemias, if any, might be due to diagnostic radiography.[40]

Tuberculosis

In the 1940s, patients with tuberculosis (TB) frequently received chest fluoroscopies during lung collapse treatment to monitor the extent of collapse and to estimate the amount of air needed to maintain the collapse. Such therapy lasted from three to five years. The average number of air injections and associated x-ray fluoroscopies often approached 100. The radiation dose to the chest marrow has been estimated to be 0.7 Gy (70 rad), 0.09 Gy (9 rad) averaged over the body. No excess leukemia was observed among 6000 exposed TB patients.[33] A RR of about 1.4 was

predicted based on the data from studies of atomic bomb survivors, suggesting that separating or splitting doses over time may lower the risk of radiation-induced leukemia, possibly by allowing cellular repair mechanisms to operate. In contrast, radiogenic breast cancers continue to occur at a high rate in these women, which suggests that organs differ in their response to fractionated doses of radiation.[13]

General Radiography

Results from studies of diagnostic radiation and adult leukemia are inconsistent. An early report from England of a positive association was later retracted when the author attributed the concentration of x-ray studies within five years prior to leukemia diagnosis to symptoms related to preclinical disease, including an increased susceptibility to infection.[129] Excesses of CML in some studies appeared to be restricted to those who received an extremely large number of x-ray studies.[43] A study at the Mayo Clinic, which included accurate estimates of bone marrow doses, found no link between leukemia and diagnostic x-ray studies, but the numbers were small.[78] A report from California found an association between diagnostic radiography, particularly x-ray studies of the lower back, and CML based on personal interviews of 136 cases and 136 neighborhood controls.[107] The largest study of diagnostic x-ray exposures and leukemia risk in adults relied on medical records of prepaid health plans in two states.[12] Information on over 25,000 x-ray studies was abstracted on 385 cases of leukemia and 1400 controls. Overall, there was a hint that leukemia risk might increase with increasing numbers of x-ray studies, but the trend was not significant. When exposures near the time of leukemia diagnosis were excluded, the trend essentially disappeared. These data were interpreted as suggesting that persons with leukemia might undergo x-ray procedures frequently just prior to diagnosis for conditions related to the development or natural history of their disease; and, again, that fractionated doses may carry a lower risk than single exposures for the same total dose. Multiple fluoroscopic chest x-ray studies did not increase the risk of leukemia among children undergoing heart catheterization.[124]

Prenatal Exposure

Most, but not all, studies of medical exposure to diagnostic x-ray studies during pregnancy are consistent with a 40-percent increased risk of childhood leukemia.[4, 81, 94, 130] Such studies are important because of the possibility that the developing fetus may be more susceptible to the leukemogenic effects of radiation than the child, as well as providing direct evidence of risk at relatively low doses of between 1 and 10 cGy. These studies have been extensively reviewed.[96, 138, 139] It had been postulated that selection factors, related to the medical reasons why women receive prenatal x-ray studies, might be responsible for the increased leukemia risk and not the x-ray exposures themselves. The absence of any childhood leukemia (and only one childhood cancer) in atomic bomb survivors exposed in utero (mean uterine dose 18 cGy[61]) supported the selection

hypothesis, as did Miller's observation[89] that it was peculiar that diagnostic x-ray studies would increase all childhood malignancies by about the same percentage (50 percent) when there is such a remarkable degree of variability between tissues in their response to radiation at other ages and because childhood cancers are known to have dissimilar origins. Biologic plausibility was questioned because children exposed under age 10 to the atomic bombs were at high risk for childhood leukemia (n = 14), but no cases of other childhood cancers occurred. Animal experiments do not suggest an enhanced sensitivity to leukemia induction following irradiation during fetal stages.[138]

Evidence against the selection hypothesis comes from the demonstration of a dose-response relationship for childhood leukemia based on number of x-ray films taken and from the observation that the excess risk was as great among twins, for whom x-ray pelvimetry was far more frequent (55 percent) than among singletons (15 percent) simply because of a greater likelihood that pelvimetry will be used to determine fetal positioning before delivery.[91] This latter observation was confirmed in a case-control study of twins born in Connecticut.[53] Nonetheless, it is argued that the number of x-ray studies is not necessarily equivalent to fetal dose and that twin studies are difficult to interpret. For example, despite substantial population exposure to prenatal x-ray studies, cohort studies consistently find twins to be at significantly low risk of childhood leukemia compared with single births.[59, 138] In fact, it is notable that only case-control studies find increased leukemia risks after prenatal exposure and that not a single cohort investigation has reported a positive finding.[23, 61, 59, 109] Although there is no reason to believe that the fetus should be immune to the leukemogenic effects of ionizing radiation, there also is little reason to believe that the risk should be substantially greater for exposures just prior to birth than for exposures in early childhood. Thus, although it is established that prenatal x-irradiation is associated with an increased risk of childhood cancer, the magnitude of the hazard, and even the causal nature of the association, remain uncertain.[80, 138]

Radionuclide Exposures

Human studies of radioactive iodine (^{131}I), phosphorus (^{32}P), and Thorotrast, a radioactive contrasting agent containing thorium (^{232}Th), have been conducted and leukemia risk evaluated.

Radioactive Iodine

Several Swedish studies have addressed cancer risks among patients administered ^{131}I, including 35,000 patients given diagnostic doses; 10,000 patients treated for hyperthyroidism; and 800 patients treated for thyroid cancer.[51, 52, 57] The half-life for ^{131}I is about eight days, and thus, the dose is delivered at a low rate over a period of about 30 days. A wide range of bone marrow doses were observed, but no trend in the RR for leukemia was seen. Again, it seems possible that a radiation dose delivered gradually over time is less leukemogenic than a brief exposure delivering the same total dose. Similarly, no excess leukemia was seen in a large cooperative study conducted in the United States of patients treated with ^{131}I for hyperthyroidism.[117] Small excesses of leukemia have, however, been reported among cancer patients treated with very high doses. In a study of 258 persons given high-dose ^{131}I for inoperable thyroid cancer, four cases of leukemia were observed versus 0.08 expected based on general population rates.[38] A slight excess of leukemia (4 versus 1.6) was reported among 834 patients treated with ^{131}I for thyroid cancer in Sweden.[52] The doses to the bone marrow and other organs in these series were large and likely between 0.5 and 1.0 Gy.

Polycythemia Vera

Among 1222 patients treated for polycythemia vera, a blood disease characterized by overproduction of red cells, leukemia developed in 11 percent of 228 patients treated with ^{32}P, 9 percent of 79 patients treated with x-rays, and 16 percent of 72 patients treated with both x-rays and ^{32}P, but only in 1 percent of 133 nonirradiated patients.[90] A randomized clinical trial found that 9 of 156 (6 percent) patients treated with ^{32}P developed leukemia, in contrast to 1 of 134 (1 percent) treated by phlebotomy.[3] Patients treated with chlorambucil were at highest risk (16 of 141, 11 percent). It is possible that the bone marrow of patients with polycythemia vera may be unusually sensitive to radiation, and it is unclear what effect the natural history of polycythemia vera might have on leukemia development.[150]

Thorotrast

Patients given Thorotrast, a radiographic contrast medium containing thorium dioxide, are at increased risk of leukemia.[2, 97, 144] The cell types include erythrocytic leukemia, which is rare, and AML and CML. These data indicate that α– particles can increase the risk of leukemia, at least those associated with a colloid of thorium oxide, which is taken up in the red marrow. These data further suggest that the distribution of dose in bone marrow is important, because leukemia excesses are not reported in radium dial painters or in patients treated with radium-224, in which the dose of α– particles is primarily to the bone surfaces and not the bone marrow.[126, 127] In these instances of radium exposure, osteosarcoma develops but not leukemia. Interestingly, the risk coefficient for α– particle–induced leukemia seems very close to that for exposure to the atomic bomb, indicating that the relative biologic effectiveness might be similar.[6]

Occupational Exposures

Leukemia following occupational exposures has been studied in radiologists and nuclear industry workers. Challenges to evaluating and quantifying the risks of radiogenic leukemia in worker studies include the usual lack of dosimetric data and the relatively low statistical power associated with low cumulative exposures.

Medical Radiation Workers

The first cancer attributed to ionizing radiation occurred on the hand of a radiologist in 1902,[96] and leukemia was first associated with chronic exposure in studies of radiologists.[82] Leukemia, aplastic anemia, and skin cancer were excessive among radiologists who practiced during the early part of this century before radiation protection guidelines were in use, but these risks appear to have disappeared among more recently employed radiologists.[76, 84, 121, 148] A recent report on 27,000 medical radiation workers in China found a significant excess of leukemia.[148] The average bone marrow dose was not known but may have been 1 Gy or more. Even today, it is not uncommon for x-ray workers in China to receive time off when their blood cell counts become severely depressed. These medical worker studies indicate that prolonged exposure of sufficient cumulative dose can result in leukemia, but the lack of dosimetry precludes quantification of risk. A new study of 140,000 radiologic technologists should provide useful information on leukemia risks in the occupational setting.[11]

Nuclear Industry Workers

The mortality experience of nearly 31,500 male and 12,600 female workers employed between 1944 and 1978 at the Hanford nuclear installation in Richland, Washington, has been reported by several investigators. The most recent analyses revealed a strong healthy worker effect; a significant deficit of cancer mortality, including leukemia; and no evidence for increasing risk with increasing film badge exposure for any cancer.[47]

Results from studies of workers at nuclear installations are generally inconsistent. The initial report of United Kingdom Sellafield workers revealed no leukemia excess, although a dose response was suggested when analysis included only exposures occurring 15 or more years prior to diagnosis.[122] Leukemia was elevated among persons employed at the Oak Ridge National Laboratory (ORNL), but risk was inversely related to dose.[47] A previous analysis of data on workers at the ORNL[151] received considerable criticism.[46] An excess of leukemia, including CLL, was highlighted even though leukemia risk decreased with increasing level of exposure. Leukemia has not been found to be elevated among plutonium workers.[146]

A recent mortality study from a large registry of 95,000 radiation workers in the United Kingdom reported significantly increased risks for leukemia, excluding CLL.[66] Risk estimates were consistent with atomic bomb survivor data but apparently not with the studies of United States workers, which were negative.[46] This first report should be interpreted with some caution because the leukemia risk was evident only at one facility, Sellafield, where high cumulative exposures over 1 Gy have occurred and where exposure to leukemogenic chemicals during fuel reprocessing activities might have occurred. Further studies of nuclear facility workers are being conducted to validate risk estimates from high-dose studies, but the limited data available to date are sufficient only to rule out the possibility of unusually high risks from low-dose fractionated exposures.

Environmental Exposures

Studies of leukemia risk associated with environmental radiation have been largely noninformative because of the generally low doses involved and the associated low statistical power to detect an effect. This is not to say that low doses of radiation are without effect, just that epidemiologic methods are just too crude to detect convincingly low-level excess risks on the order of 20 to 30 percent.[74] Analytic studies have been conducted on persons exposed to high levels of natural background radiation, persons living near nuclear installations, populations exposed as a result of nuclear reactor accidents, and persons exposed to radon.

Natural Background Radiation

Correlation studies attempting to link leukemia incidence or mortality with natural background radiation have generally been interpreted as negative[24, 63, 83, 147] but are fraught with uncertainties regarding dose levels, migration patterns, selection factors for place of residence, and geographic variations in the accuracy of cancer diagnoses.[105, 125] In England, childhood cancer was correlated with maternal irradiation from background sources,[72] but interpretation of a causal link is clouded by the serious limitations of ecologic correlation analyses.[96] The most extensive investigation of the possible health effects of naturally occurring radiation was conducted in China on a stable population of 73,000 persons who received three times the amount of background radiation (330 milliroentgens (mR)/yr versus 110 mR/yr) as 77,000 inhabitants of a comparison region. Differences in chromosome aberrations in circulating lymphocytes indicated that the background radiation levels were meaningfully different.[149] Leukemia, however, was not increased among residents of the high background area.[19]

Surveys Around Nuclear Facilities

Reports of small clusters of childhood leukemia around nuclear installations in the United Kingdom in the 1980s prompted several large-scale systematic surveys. Lymphoid leukemia among persons under age 25 was found to be generally increased in populations living near nuclear fuel reprocessing or weapons production facilities in the United Kingdom but not in populations living near plants that generated electricity.[20, 42] Mortality from Hodgkin's disease at ages 0 to 24 also was increased, whereas mortality from lymphoid leukemia at ages 25 to 64 was significantly reduced. There was no overall increase in cancer mortality in the vicinity of nuclear installations.

Interestingly, a study from Britain evaluated residents of areas where construction of nuclear power stations had only been considered or just recently completed. Excesses of childhood leukemia and Hodgkin's disease, as well as deficits of adult leukemia, were reported that were similar to those previously identified in areas with operating nuclear facilities.[21] The authors concluded that the unexpected increases in some childhood cancers around nuclear

installations are unlikely to be due to environmental radiation pollution but rather to other risk factors yet to be identified. An infectious agent associated with large immigrations of people into those areas, for example, has been proposed as one possible explanation (see also Chapter 8 on this topic).[69, 70]

In the largest ecologic survey to date, cancer mortality in 113 counties in the United States that contained or were adjacent to 62 nuclear facilities was compared with mortality in control counties with similar population and socioeconomic characteristics; 2,700,000 cancer deaths were included.[62] Overall, and for specific groups of nuclear installations, there was no evidence that mortality for any cancer, including childhood leukemia, was higher in counties with nuclear reactors than in the control counties. For childhood leukemia, the RR in the study counties versus their controls after plant start-up was 1.03, whereas before start-up it was 1.08. For all leukemia, the RRs were 0.98 after start-up and 1.02 before. Systematic studies in France, Germany, and Canada also failed to identify excesses of childhood leukemia among populations residing near nuclear facilities.[56, 85, 87]

Clusters Around Nuclear Facilities

In 1983, a team of investigative television reporters from Yorkshire set out to evaulate the risk of cancer among workers at the Sellafield (Windscale) nuclear fuel reprocessing complex in West Cumbria, United Kingdom. Learning that neither cancer nor leukemia was excessive in these workers,[122] the reporters focused on an apparent cluster of seven young people who developed leukemia between 1950 and 1983 in Seascale, a village about 3 km south of Sellafield. A government report confirmed that childhood leukemia was elevated (4 observed versus 0.25 expected) in the region near Sellafield.[5] An assessment of total radiation exposure of the local population revealed that natural background contributed the greatest amount (66 percent) and Sellafield discharges only 16 percent. Thus, environmental pollution from radioactive releases seemed an unlikely culprit.[28] Additional studies found that the excess of leukemia occurred entirely among individuals born in Seascale (5 versus 0.53) and not among children born elsewhere (0 versus 0.54), suggesting that factors present in early life or before birth might be important.[43] A subsequent case-control study, discussed later, raised the possility that parental occupational exposure among Sellafield workers might explain the cluster.[44] Recently, it was determined that a significant excess of leukemia also occurred among young people born in places other than Seascale, minimizing the possible role that preconception irradiation might have played overall.[67]

Other studies around nuclear facilities have failed to provide clear insights into the reasons for apparent clusterings of childhood cancer.[36, 79] In some investigations, findings entirely depended on the selection of particular geographic and calendar time groupings. Even the Seascale cluster might be considered suspect, because it was the *occurrence of the cases* that determined both the geographic boundary and the age definition of the cluster. Recall that the TV reporters first went to Sellafield, not Seascale, and were seeking excesses of cancer among adult workers, not leukemia among young people in the general population.

Preconception

The most provocative (and controversial) finding from the Seascale studies was the association between leukemia and preconception irradiation of the fathers working at Sellafield.[44] If true, the apparent cluster might be explained in terms of occupational rather than environmental radiation exposure. The study, however, is at odds with the prospective investigation of children of the atomic bomb survivors for whom no excesses of cancer, chromosome aberrations, or genetic mutations in blood proteins were observed.[99, 100, 138] Other case-control studies in England, Scotland, and Canada have failed to confirm the association between paternal preconception radiation and childhood leukemia.[70, 86, 110, 142] Further, a recent study of 10,363 children who were born to fathers who worked at Sellafield evaluated the geographic distribution in Cumbria of the paternal dose received prior to conception.[103a] Paternal doses were consistently higher among fathers of children born outside Seascale. Because childhood leukemia was not increased in these areas of West Cumbria despite the higher preconception exposures, the authors concluded that paternal exposure to radiation before conception is, in itself, unlikely to be a sufficient causal factor for childhood leukemia.

An alternative hypothesis being pursued to explain the apparent clusters is that childhood leukemia may occur as a rare response to an unidentified infection whose transmission is facilitated when large numbers of people from different geographic areas come together, such as might occur when large industrial complexes are built in rural areas (see also Chapter 8).[68–70]

Nuclear Reactor Accidents

The nuclear reactor accident at Three Mile Island released little radioactivity into the environment, much less than the annual population exposure to natural background. Any presumed increase in cancer at these levels would be negligible and undetectable,[140] and not surprisingly, no peculiar mortality patterns have been noted.[62] In contrast, the accident at Chernobyl resulted in a massive release of radioactivity.[138] Studies of surrounding populations to date have not linked the release to increases in childhood leukemia,[104] and it remains to be determined whether populations residing outside the immediate vicinity of the reactor complex would have received sufficient exposure to result in a detectable increase in leukemia.[77] On the other hand, 600,000 workers were sent to Chernobyl after the accident to clean up the environment and entomb the reactor. Allowable occupational exposures for the workers were stated to be 0.35 Gy, suggesting that doses might have been high enough for future health studies to be informative. Recently, it was revealed that an explosion in 1957 in a storage tank at the Chelyabinsk nuclear facility (the Kyshtym accident) in the former Soviet

Union released large amounts of radioactive waste into the Techa river. High-level radioactive effluents also had been dumped into the river prior to the accident between 1949 and 1956.[73] Population doses among 28,000 residents were as high as 4 Gy, and leukemia was reported to be significantly increased based on 37 cases.[138]

Radon

Estimates of environmental radon exposures in England have been correlated with monocytic and other types of leukemia (but not lung cancer).[37, 55] The link was not confirmed, however, in a separate analysis using smaller geographic units.[95] The possibility that high levels of radon might be related to human leukemia seems unlikely because underground miners heavily exposed to radon have been found to be at high risk for lung cancer but not leukemia.[133]

Nonionizing Electromagnetic Fields

Extremely low-frequency electromagnetic fields (EMF) (60 Hz) from household appliances or electrical power transmission lines do not possess enough energy to strip electrons from atoms. Although they are generating great public concern, exposures to nonionizing radiations have not been convincingly linked to leukemia in humans or animals, and the evidence to date is sufficient only to formulate hypotheses for testing in future studies.[102] Risk of childhood leukemia was recently evaluated in three Nordic studies.[1] An apparent excess of leukemia was based on a total of 13 cases that occurred over a period of over 20 years. Associations were reported for estimated field strengths based on proximity to transmission lines and power consumption but not for measured magnetic fields. Differences in the methods used to estimate relevant EMF exposure, in the categorization of EMF exposure (cut points), and in the selected time relationships between exposure and leukemia diagnosis make interpretation of a causal association based on such small numbers tenuous at best. Thus, no causal relationship has been established between EMF and childhood leukemia, and results of ongoing large-scale case-control studies in the United Kingdom, Canada, and the United States will be of great interest.[34]

GENERALIZATIONS

Human studies of radiation-induced leukemia (see Table 11–2) have revealed the complex nature of the relationship between exposure and leukemia occurrence. Recognizing the differences in such studies, several generalizations can be made, nonetheless.

1. Radiation-induced leukemia is reported more frequently than any other cancer, owing largely to a short minimum latency period and a high RR coefficient.

2. The time response appears to be wavelike, peaking from three to ten yeas after exposure. Radiogenic leukemias occur much earlier than radiogenic solid tumors.

3. Age at exposure is an important determinant of risk, with the young apparently being the most sensitive on a relative scale.

4. Different cell types vary in their response to radiation, and one common type of leukemia, CLL, has never been linked to radiation.

5. The exposure-response relationship appears to be nonlinear, with risk per unit dose being lower at low doses than at high doses.

6. At very high doses to limited volumes of tissues, cell killing may predominate over cell transformation. Secondary leukemia does not appear to be a common event after radiotherapy for cancer, but small excesses on the order of two-fold have been observed. The excesses are much lower than predicted from studies of atomic bomb survivors.

7. The mechanism for radiation-induced leukemia likely involves chromosomal rearrangements.

8. Fractionation or splitting of exposures over time also may lower risk appreciably, but more study is needed to clarify the magnitude of the risk reduction in humans.

9. The fetus appears vulnerable to the carcinogenic action of ionizing radiation, but whether the level of risk differs from that in young children is not entirely clear.

10. α– Particles (helium nuclei) in some circumstances can cause leukemia, but the unusual distribution of dose from Thorotrast in the bone marrow may be a special case. Radium and radon have not been linked to leukemia.

11. Very low radiation doses received from environmental exposures are difficult to tie to increased leukemia risks, because the anticipated excesses are so small in relation to natural occurrence.

12. The evidence that preconception radiation increases leukemia risk in offspring is weak.

FUTURE RESEARCH

The quantitative description of risk continues to present unique opportunities for research that may lead to a better understanding of the pathogenesis of cancer in humans, with implications for public health and the setting of radiation protection standards. Studies of populations exposed occupationally to ionizing radiations may provide valuable insights into the effects of low doses received at low-dose rates. New biologic markers of exposure, such as the glycophorin-A mutational assay for red blood cells and fluorescent in situ hybridization for chromosome aberration detection, may offer new possibilities for quantifying prior exposures.[131] It remains to be learned whether molecular mechanisms in radiation leukemogenesis are the same as for de novo leukemias. The interaction of radiation with other leukemogenic exposures, such as chemotherapeutic agents, might reveal interesting mechanistic understandings. It remains puzzling why CLL, a common type of adult leukemia, has never been linked to ionizing radiation. It is unclear whether there are sensitive subgroups within the population who are at especially high risk for radiation-induced leukemia. New information about the human genome may permit a greater understanding of the genetic events leading to radiogenic leukemia.

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